

This listing of the claims replaces all prior versions in the application.

**Listing of Claims:**

1-42 (Canceled)

43. (Currently Amended) A detection system for detecting fluorescence in a body of a subject associated with an administered fluorescent analyte, the fluorescent analyte including at least one of a fluor-labeled analyte, a naturally fluorescent analyte and an analyte that exhibits fluorescence when administered to the subject, the detection system comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor comprising at least one excitation light source held therein, the excitation light source being configured to emit a fluorescent excitation light signal used to generate a fluorescent response of the fluorescent analyte in local tissue, wherein the sensor projects the excitation light signal outside the sensor at a distance sufficient to probe fluorescent activity at locations away from the sensor of several millimeters, with the fluorescent excitation light signal having a wavelength that is at least about 400 nm to about 900 nm, and to detect fluorescence from the fluorescent analyte in the local tissue in the body in response to the emitted excitation light signal, at least intermittently, over a period of time extending for at least about 24 hours after administration of the fluorescent analyte to the subject, wherein the fluorescent analyte is internally administered from a source other than the at least one sensor; and

a processor operably associated with the at least one sensor configured to direct the output of the excitation signal and to receive fluorescence intensity signal data associated with the detected fluorescence of the administered analyte in response to the excitation light signal at the fluorescence excitation wavelength from the at least one sensor, wherein said processor is configured to monitor intensity of the detected fluorescence over time and determine at least one of the following: a pharmacokinetic, a pharmacodynamic, or a biokinetic response to the internally administered fluorescent analyte and/or local bioactivity based on the monitored intensity  $[[r]]$  over at least one monitoring period.

44. (Previously Presented) A system according to Claim 43, wherein the sensor is configured as an implantable telemetric sensor having an elongated substantially cylindrical body, and wherein the sensor is configured to emit excitation light into local tissue at a tumor treatment site at a depth in the local tissue so that the excitation light penetrates layers of fascia that encapsulate the sensor and/or through fibroblasts having thicknesses of between about 50-100  $\mu\text{m}$ .

45. (Original) A system according to Claim 44, wherein the sensor has a body with a diameter of about 3 mm or less.

46. (Previously Presented) A system according to Claim 43, wherein the at least one sensor is configured to wirelessly transmit signals associated with the *in vivo* detected fluorescence at predetermined intervals extending over a monitoring period having a duration at least about 1 week followed by a dormant period of at least one week.

47. (Original) A system according to Claim 46, wherein the at least one sensor is configured to wirelessly transmit signals associated with the *in vivo* detected fluorescence at predetermined intervals, including a plurality of transmissions over a plurality of days during a monitoring period having a duration of at least about 1 month.

48. (Currently Amended) A system according to Claim 43, wherein the at least one sensor is a plurality of sensors, including first and second sensors that are adapted to detect fluorescence emitted from first and second spatially separate locations in the subject, and wherein the system processor is configured to monitor fluorescence detected by each of the first and second sensors to provide data for assessing a treatment.

49. (Original) A system according to Claim 43, wherein the at least one sensor is a plurality of sensors configured to be individually operable, and wherein the processor is configured to poll each one separately.

50. (Original) A system according to Claim 48, wherein the first location is associated with normal or non-diseased tissue and the second location is associated with diseased, abnormal, or cancerous tissue.

51. (Previously Presented) A system method according to Claim 43, wherein the sensor is configured to generate excitation light that is able to penetrate tissue up to about 20 mm away.

52. (Original) A system according to Claim 43, wherein the sensor is configured to generate excitation light signals having a wavelength of from about 400 to about 660 nm.

53. (Original) A system according to Claim 52, wherein the sensor is configured to detect fluorescence response wavelengths of from about 400 to about 695 nm.

54. (Original) A system according to Claim 43, wherein the at least one sensor is adapted to be implanted in the body at subsurface depths up to about 25 cm.

55. (Original) A system according to Claim 43, wherein the sensor comprises laser diode that is configured to generate the excitation light.

56. (Original) A system according to Claim 55, wherein the laser diode is operated in a pulsed manner to generate the excitation light.

57. (Original) A system according to Claim 56, wherein the pulsed laser diode is operated between at a frequency of from about 10Hz to about 1 KHz with a duty cycle of between about 1-10%.

58. (Original) A system according to Claim 56, wherein the laser diode is configured to generate an excitation signal with a power level of from about 1 to about 20mW.

59. (Currently Amended) A system according to Claim 43, wherein the system is configured to generate a plurality of signals having a predetermined stepwise variation in power, and wherein the processor comprises computer readable program code that generates optical profiling data using the detected fluorescence generated in response to the generated signals with the stepwise variation in power ~~thereto is used to generate optical profiling data.~~

60. (Original) A system according to Claim 44, wherein the sensor further comprises a detector, and wherein the sensor body comprises a cylindrical optical filter formed on the wall thereof that selectively allows light associated with the fluorescent wavelengths of interest to travel into the interior of the sensor body to the detector.

61. (Original) A system according to Claim 60, wherein the sensor further comprises a compound filter aligned with the laser diode to allow the excitation light to exit the sensor body through the cylindrical filter.

62. (Original) A system according to Claim 60, wherein the sensor further comprises an optical window aligned with the laser diode to allow the excitation light to exit the sensor body through the cylindrical filter.

63. (Original) A system according to Claim 60, wherein the detector is substantially centrally located in the sectional width of the sensor body.

64. (Original) A system according to Claim 63, wherein the sensor is configured to allow fluorescence to enter and engage with the detector having a width that is between about  $1.15 R$  to about  $0.54 R$ , where "R" is the radius of the cross-section of the sensor body, and

wherein the cylindrical filter extends substantially continuously over the perimeter of the sensor body at a length that is less than the length of the sensor body.

65. (Original) A system according to Claim 43, wherein the excitation source comprises a laser diode and the detector comprises a photodiode, wherein the sensor body is a glass sensor capsule, and wherein the sensor further comprises epoxy that is index-matched to couple the laser diode and photodiode to the glass capsule enclosing the detector and diode to inhibit internal reflections.

66. (Original) A system according to Claim 65, wherein the sensor further comprises a second detector, wherein the first detector is operably associated with a filter that selectively allows fluorescent light signals to pass therethrough, and wherein the second detector is configured to detect excitation light signals, and wherein data from the second detector is used to normalize the data from the first detector.

67. (Original) A system according to Claim 66, wherein the sensor further comprises a second detector, and wherein the first and second detectors are held in side-by-side alignment in the sensor body.

68. (Original) A system according to Claim 67, wherein the sensor further comprises a second detector, and wherein the first and second detectors are held in back-to-back alignment.

69. (Original) A system according to Claim 43, wherein the excitation source comprises first and second diode lasers operating at different excitation wavelengths and/or power.

70. (Previously Presented) A system according to Claim 43, wherein the at least one excitation light source operates with a power of less than about 20 mW, wherein the fluorescence sensor is implantable and includes:

an elongated substantially cylindrical sensor body;  
a cylindrical optical filter formed over the outer surface of the elongated sensor body; and  
at least one detector held in the sensor body configured to detect fluorescence at predetermined wavelengths of interest,

wherein the sensor is configured to be intermittently operated at plurality of sampling intervals over a monitoring period.

71. (Previously Presented) A system according to Claim 70, wherein the implantable sensor excitation source comprises a laser diode operated at a power between about 1-20mW.

72. (Previously Presented) A system according to Claim 70, wherein the sensor body comprises an optical window formed on the wall thereof to allow the excitation light to exit the sensor through the cylindrical filter.

73. (Previously Presented) A system according to Claim 70, further comprising a compound filter aligned with the excitation light source and formed about a portion of the cylindrical filter to allow the excitation light to exit the sensor through the cylindrical filter.

74. (Previously Presented) A system according to Claim 70, wherein the light source is positioned in the sensor body proximate the cylindrical wall at a distance and position that directs the excitation light out through the cylindrical filter at an angle greater than the critical angle to thereby allow the excitation light to exit the sensor through the cylindrical filter.

75. (Previously Presented) A system according to Claim 43, wherein the sensor is inductively powered, wherein the sensor comprises at least one internal optical filter and a detector configured to detect fluorescence at predetermined wavelengths of interest, and

wherein the at least one internal optical filter resides in the sensor body directly over the detector.

76. (Previously Presented) A system according to Claim 70, wherein the sensor comprises a detector without a filter that detects light that reenters the sensor while the at least one detector is in communication with a filter and detects the fluorescent light at the wavelengths of interest, and wherein the system is configured to monitor unfiltered intensity light.

77. (Previously Presented) A system according to Claim 70, wherein the sensor is configured to output a plurality of excitation light signals at a pulse duration in a millisecond range and detect fluorescence locally in response thereto over desired intervals over at least 24 hours for each monitoring period.

78. (Previously Presented) A system according to Claim 70, further comprising an anti-reflectance layer in the sensor body intermediate the wall of the sensor body and the underside of the detector.

79. (Previously Presented) A system according to Claim 43, wherein the sensor comprises a laser diode that is operated in a pulsed manner at a frequency between 10-1000 times per second to generate the excitation light.

80. (Previously Presented) A system according to Claim 79, wherein the pulsed laser diode is operated between at a frequency of between about 10-1KHz with a duty cycle of between about 1-10%.

81. (Currently Amended) A system according to Claim 70, wherein the sensor is configured to generate a plurality of excitation signals having a predetermined stepwise variation in intensity, and wherein the processor is configured to generate optical profiling data based on the detected fluorescence generated in response thereto is used to generate

optical profiling data to the excitation signals generated with the stepwise variation in intensity.

82. (Previously Presented) A system according to Claim 70, wherein the detector is substantially centrally located in the sectional width of the sensor body.

83. (Previously Presented) A system according to Claim 70, wherein the sensor is configured to allow fluorescence to enter and engage with the detector, with the detector having a width that is between about  $1.15 R$  to about  $0.54 R$ , where "R" is the radius of the cross-section of the sensor body.

84. (Previously Presented) A system according to Claim 70, wherein the cylindrical filter extends substantially continuously over the perimeter of the sensor body at a length that is less than the length of the sensor body.

85. (Previously Presented) A system according to Claim 70, wherein the sensor further comprises a second detector.

86. (Previously Presented) A system according to Claim 85, wherein the first and second detectors are held in side-by-side alignment in the sensor body.

87. (Previously Presented) A system according to Claim 85, wherein the first and second detectors are held in back-to-back alignment.

88. (Previously Presented) A system according to Claim 70, wherein the excitation source comprises first and second diode lasers operating at different excitation wavelengths and/or power.

89-104 (Canceled)



105. (Previously Presented) A detection system for detecting fluorescence in a subject associated with an administered fluorescent analyte, the fluorescent analyte including at least one of a fluor-labeled analyte, a naturally fluorescent analyte and an analyte that exhibits fluorescence when internally administered to the subject, the detection system comprising:

at least one implantable fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit an excitation light signal having a fluorescent excitation wavelength of at least 400 nm to about 900 nm at a depth into local tissue at a tumor treatment site in the subject's body so that the excitation light penetrates layers of fascia that may encapsulate the sensor and/or through fibroblasts having thicknesses of between about 50-100  $\mu\text{m}$  and to detect fluorescence from a fluorescent analyte in the local tissue beyond the layers of fascia in response to the emitted excitation light signal, wherein the at least one implantable sensor can probe fluorescent activity at subsurface locations in the local tissue that is several millimeters away from the sensor, at least intermittently, over a period of time extending for at least about 24 hours after administration of a fluorescent analyte during each monitoring period, and wherein the sensor is configured to detect fluorescence from a fluorescent analyte that is systemically administered; and

a processor operably associated with the at least one sensor configured to direct the output of the excitation signal and to receive fluorescence intensity signal data associated with the detected fluorescence in the local tissue from the at least one sensor, wherein said processor is configured to monitor intensity over time associated with one or more of the uptake and retention of the fluorescent analyte in the local tissue at a plurality of points in time over at least one monitoring period.

106. (Previously Presented) A system according to Claim 43, wherein the at least one sensor is an implantable fluorescence sensor, comprising:

an elongated substantially cylindrical sensor body;

a substantially cylindrical optical filter formed over the outer surface of the elongated sensor body and/or an internal optical filter residing inside the sensor body; and

at least one detector held in the sensor body configured to detect fluorescence at predetermined wavelengths of interest,

wherein the sensor is configured to be intermittently operated at plurality of sampling intervals over the monitoring period, and wherein the at least one sensor is configured to transmit the fluorescent excitation light signal into local tissue at a tumor treatment site in the subject's body so as to project through fascia or fibroblasts on the sensor and penetrate local tissue.

107. (Previously Presented) A detection system according to Claim 43, wherein the at least one sensor is configured to generate excitation light signals at a plurality of wavelengths between 400 nm to 900 nm, and wherein the at least one sensor is configured to emit the fluorescent light signal at the excitation wavelength at sufficient power to penetrate local tissue at up to about 20 mm away from the sensor.

108. (Previously Presented) A detection system according to Claim 43, wherein the processor is configured to analyze the detected intensity over time and predict whether a subject will have a favorable response to a cancer therapy.

109. (Previously Presented) A detection system according to Claim 43, wherein the fluorescent analyte is a fluor-labeled analyte.

110. (Previously Presented) A detection system according to Claim 43, wherein the fluorescent analyte comprises a fluor-labeled antibody, and wherein the processor is configured to monitor the intensity over time to confirm antibody attachment to a target tumor site.

111. (Previously Presented) A detection system according to Claim 43, wherein the fluorescent analyte comprises a fluor-labeled chemotherapeutic agent.

112. (Previously Presented) A detection system according to Claim 43, wherein the processor is configured to calculate a dose of a chemotherapeutic agent received at local tissue based on the intensity data intensity over time based on a correlation with a priori reference data.

113. (Previously Presented) A detection system according to Claim 43, wherein the processor is configured to predict a bioresponse to a chemotherapeutic agent received at the local tissue based on the detected intensity over time.

114. (Previously Presented) A detection system according to Claim 43, wherein the sensor is configured to transmit all excitation signals at wavelengths of between about 630-660 nm.

115. (Previously Presented) A detection system according to Claim 43, wherein the at least one sensor has a sensor wall with a surface that is configured to allow excitation and response light to be transmittable through the sensor wall, and wherein the sensor excites and detects fluorescence from the fluorescent analyte in local tissue through a layer of fibroblasts and/or fascia encapsulating the sensor.

116. (Previously Presented) A detection system according to Claim 43, wherein the processor is configured to determine a dose of the fluorescent analyte in the local tissue based on an intensity response profile that is correlated to a priori data of known reference values to determine the delivered in vivo dose.

117. (Previously Presented) A detection system for detecting fluorescence in a patient's body associated with an administered fluorescently labeled chemotherapeutic agent, the detection system comprising:

at least one implantable fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal between about

400 nm to about 900 nm and to detect fluorescence from a fluorescently labeled chemotherapeutic agent in localized tissue in the body in response to the emitted excitation light signal, at least intermittently, over an active monitoring period of time extending for at least about 24 hours after administration of the fluorescently labeled chemotherapeutic agent, wherein the at least one sensor is dormant between successive active monitoring periods; and a processor operably associated with the at least one implantable sensor configured to direct output of the excitation signal to local tissue and to receive fluorescence intensity signal data associated with the locally detected fluorescence of the chemotherapeutic agent from the at least one sensor, wherein said processor includes computer readable program code for monitoring fluorescence intensity over time of the detected fluorescence associated with one or more of the uptake and retention of the fluorescently labeled agent in target localized tissue at a plurality of points in time over at least one monitoring period, and wherein the processor includes computer readable program code that calculates a dose of the chemotherapeutic agent in the localized tissue and/or that determines a patient's likely therapeutic response to the chemotherapeutic agent based on the detected fluorescence.

118. (Previously Presented) A detection system according to Claim 117, wherein the chemotherapeutic agent comprises an antibody, and wherein the system is configured to activate the sensor during a monitoring period that starts proximate in time to the administration of the chemotherapeutic agent and continues for a predetermined amount of time or continues for as long as a detected fluorescence count associated with the administered chemotherapeutic agent is above a defined threshold.

119. (Currently Amended) A detection system for monitoring pharmacokinetics and/or pharmacodynamics in a subject associated with an administered fluorescently labeled analyte, the detection system comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal at a wavelength of at least about 400 nm to about 900 nm and to detect fluorescence from the fluorescently labeled

analyte in localized tissue at a target site in the body in response to the emitted excitation light signal; and

a processor operably associated with the at least one sensor, the processor comprising a computer readable storage medium having computer readable program code embodied in the medium, the computer readable program code comprising:

computer readable program code for directing ~~configured to direct~~ output of the excitation signal to the target site and to receive the detected fluorescence intensity signal data; and

~~, wherein said processor is configured to~~ computer readable program code that monitors fluorescence intensity of the fluorescently labeled analyte in the localized tissue at a plurality of points in time over at least one monitoring period and determines the pharmacokinetics and/or pharmacodynamics at the target site.

120. (Currently Amended) A detection system according to Claim 119, wherein the fluorescently labeled analyte is configured to increase or decrease in response to a level of protein or other defined cellular production.

121. (Currently Amended) A detection system according to Claim 119, wherein the detection system is configured to monitor a patient that has undergone gene therapy, and wherein the system processor computer readable program code comprises computer readable program code that ~~that~~ [[to]] monitors fluorescence intensity at the target treatment site in subsequent generations of cells after a gene therapy treatment.

122. (Currently Amended) A detection system according to Claim 119, wherein the processor comprises computer readable program code that is configured to detect fluorescence of the fluorescently labeled analyte to confirm micelle concentration.

123. (Currently Amended) A system for determining a phenotypic response of a patient to a selected drug therapy, comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal at a wavelength of at least about 400 nm to about 900 nm and to detect fluorescence from an internally administered fluorescently labeled therapeutic agent in localized tissue at a target site in the body in response to the emitted excitation light signal; and

a processor operably associated with the at least one sensor, the processor comprising a computer readable storage medium having computer readable program code embodied in the medium, the computer readable program code comprising:

computer readable program code that configured to direct output of the excitation signal to the target site and to receive the detected fluorescence intensity signal data; and

wherein said processor is configured computer readable program code that to monitors fluorescence intensity of the fluorescently labeled therapeutic agent in the localized tissue at a plurality of points in time over at least one monitoring period and predicts a phenotypic response of the patient to the therapeutic agent at the target site.

124. (Currently Amended) A system according to Claim 43, wherein the system processor is configured to generate a fluor-intensity measurement profile summary of the subject based on the monitored intensity.